Remarks

I. The Amendments

The specification of the application was amended by entering a sequence listing. The newly entered sequence listing is separately numbered from the rest of the pages of the application and should be entered after the claims and abstract.

In addition, the application, as it appears in the English translation, was amended to include sequence identification numbers for DNA sequences.

II. Submission of Computer Readable Copy of Sequence Listing

Applicants are including herewith a 3.5 inch computer readable diskette which contains a copy of the newly submitted Sequence Listing in ASCII text.

III. Statements to Comply With 37 C.F.R. § 1.821 and 1.825

In compliance with 37 C.F.R. § 1.821(f), Applicants' undersigned attorney hereby states that the content of the paper and computer readable copies of the Sequence Listing submitted herewith are the same. In accordance with 37 C.F.R. § 1.821(g), Applicants' undersigned attorney hereby states that the submission herewith does not add new matter to the application.

Conclusion

In light of the present amendments and enclosures, Applicants respectfully submit that all Sequence Listing requirements have now been complied with. It is therefore respectfully submitted that this application is now in condition for substantive review.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (703) 905-2173.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: Michael A. Sanzo

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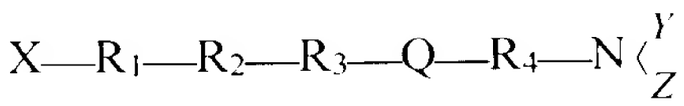
Appendix

Version with Markings to Show Changes Made

The specification of the application was amended to enter sequence identification numbers. The changes that were made are shown below with the underlined words indicating text that was added. The text in brackets was removed.

On page 3 of the specification, paragraph 2 were amended as follows:

In its first aspect, the compounds of the present invention are represented by formula (A):



(A)

with peripheral analgesic effect, wherein: X is selected from the group consisting of H and C_{1-6} alkyl; Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C_{1-6} alkyl; R_1 is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue; R_2 is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine; R_3 is an aromatic amino acid; R_4 is an aromatic amino acid residue; Q is an amide bond or an interposed amide bond mimetic; with the following provisos: a) when R_1 is a tyrosyl residue; R_2 is D-alanine; X, Y, and Z, are H; and R_3 is phenylalanine; then R_4 is not unsubstituted phenylalanine or phenylalanine substituted with $4NO_2$ or $4N_3$; b) when R_1 is a tyrosyl residue; R_2 is D-alanine; X, Y, and Z are H; and R_4 is phenylalanine; then R_3 is not unsubstituted phenylalanine or phenylalanine substituted with $4NO_2$; c) when R_1 is a tyrosyl residue; R_2 is D-alanine; X, Y, and Z are H; and R_4 is 1'-naphthylalanine; then R_3 is not 1'-naphthylalanine or 2'-naphthylalanine; d)

with a lower alkyl or lower thioalkyl group as a side chain, and R_4 is a neutral

amino acid; then R_3 is not unsubstituted phenylalanine; and wherein said compound is not selected from the group consisting of: H-Tyr-D-Phe-Phe-Phe-NH_2; H-Tyr-D-NMePhe-Phe-Phe-NH_2; H-Tyr-D-Tic-Phe- Phe-NH_2; H-Tyr-Pro-Phe-Thr(Bzl)-NH_2 (SEQ ID NO:2); H-Tyr-Pro-Phe-Phe-NH_2 (SEQ ID NO:1); H-Tyr-Pro-Phe-Apb-NH_2; H-Tyr-Pro-Phe-App-NH_2; H-Tyr-Pro-Phe-Aph-NH_2; and H-Tyr-Pro-Apb-Phe-NH_2: wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenyl pentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

On page 9 of the specification, the last paragraph which ends in page 11 was amended as follows:

Specific, individual, preferred compounds of this invention are as follows: H-Tyr-Aib-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-2'-Nal-NH_2;

H-Tyr-D-Ala-D-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe($4NO_2$)-Phe($4NO_2$)-NH_2;

H-Tyr-D-Ala-Phe-Tic-NH_2;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH_2;

H-Tyr-D-Ala-Phe-1'-Nal-NH_2;

H-Tyr-D-Ala-Trp-Phe-NH_2;

H-Tyr-D-Ala-Phe-Trp-NH_2;

H-Tyr-ΨAla-Phe-Phe-NH_2; (SEQ ID NO:3)

ΨCH_2-Tyr-D-Ala-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Trp-NH_2;

H-Tyr-D-Nle-Phe-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-Phe-NH_2;

H-Tyr-D-Nle-Trp-Trp-NH_2;

H-Tyr-D-Nva-Phe-Phe-NH_2;

H-Tyr-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Val-Phe-Phe-NH_2;

H-Tyr-D-Leu-Phe-Phe-NH_2;

H-Tyr-D-Ile-Phe-Phe-NH_2;

H-Tyr-D-Abu-Phe-Phe-NH_2[']$_2$

H-Tyr-Chl-Phe-Phe-NH_2;

H-Tyr-Cle-Phe-Phe-NH_2;

H-Tyr-D-Arg-Phe-Phe-NH_2;

H-Tyr-D-Cys-Phe-Phe-NH_2;

H-Tyr-D-Thr-Phe-Phe-NH_2;

H-DMT-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;

H-Tyr-D-Ala-Phe-Phg-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Hph-NH_2 bis-trifluoroacetic acid;

H-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid;

H-D-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Hph-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Cys(Bzl)-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Hph-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Arg-Phg-Phe-NH_2 bis-trifluoro acetic acid salt;

H-Tyr-D-Ala-Phe-Phe-CH_2OH hydrochloride salt;

H-Tyr-D-Ala-Hph-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Met-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-D-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Ala-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-(D)-Ala-(D)-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Phe(pF)-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-D-Phe(pF)-NH_2 ditrifluoroacetic acid salt;

On page 19 of the specification, Table 1 was amended as follows:

Table 1

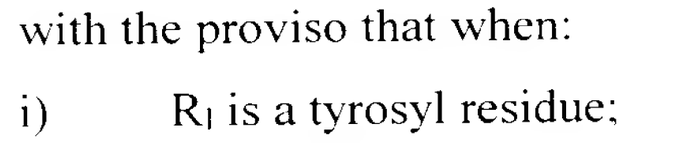
Sequence	Ki^{μ} [nM]	Ki^{δ}/Ki^{μ}	GPI(IC_{50}) [nM]	ED_{50}(PBQ) mg/k (20min)	Hot Plate mg/kg
H-Tyr-D-Ala-Phe-Phe-NH_2	1.53	409	3	1.4	>100
H-Tyr-D-Phe-Phe-Phe-NH_2	3.63	37.7	247	>20	
H-Tyr-Aib-Phe-Phe-NH_2			73	>20	
H-Tyr-D-Nle-Phe-Phe-NH_2	0.968	373	15	2.5 (5 min.)	
H-Tyr-Pro-Phe-Phe-NH_2 (SEQ ID NO:1)	4.10	182	15	>20	
H-Tyr-D-Ala-Phe-2'-Nal-NH_2	0.655	119	2	1.1 (5 min.)	
H-Tyr-D-Ala-2'-Nal-1'-Nal-NH_2	5.61	102	-	>20	
H-Tyr-D-Ala-D-Phe-Phe-NH_2	26.0	82.7	925		
H-Tyr-D-Ala-Phe-Phe(4-NO_2)-NH_2	0.509	129	8	4	
H-Tyr-D-Ala-Phe(4-NO_2)-Phe(4-NO_2)-NH_2	0.826	570	6	>20	
H-Tyr-D-Ala-Phe-Phe(4-N_3)-NH_2	1.49	107	50		
H[.]-Tyr-D-Ala-Phe(4-NO_2)-Phe-NH_2	56.8	24.3	77		
H-Tyr-D-Ala-Phe-Tic-NH_2	12.7	279	-		
H-Tyr-D-Ala-Phe-Phe(NMe)-NH_2	22.6	215	241		
H-Tyr-D-Ala-Phe-1'-Nal-NH_2	0.981	174	2	>20	

e 20 of the specification, continuation of Table 1 was amended as follows:

BCH#	Sequence	Ki$^{\mu}$ [nM]	Kiδ/Ki$^{\mu}$	GPI(IC_{50}) [nM]	ED_{50}(PBQ) m/k (20min)	Hot Plate m/k
1783	H-Tyr-D-Ala-l'-Nal-l'-Nal-NH_2	2.88	410	-	>20	
1784	H-Tyr-D-Ala-Trp-Phe-NH_2	3.57	238	20	>20	
1785	H-Tyr-D-Ala-Phe-Trp-NH_2	2.21	214	16	>20	
1786	H-Tyr-D-Ala-Trp-Trp-NH_2	0.833	783		10	
1787	H-Tyr-VAla-Phe-Phe-NH_2 (SEQ ID NO:3)				10	
2202	∇CH_2Tyr-D-Ala-Phe-Phe-NH_2				>10	
2208	H-Tyr-D-Nle-Phe-Trp-NH_2				>3	
2211	H-Tyr-D-Nle-Phe-2'-Nal-NH_2				>10	
2212	H-Tyr-D-Nle-Trp-Phe-NH_2				>10	
2213	H-Tyr-D-Ala-Trp-2'-Nal-NH_2				>5	
2214	H-Tyr-D-Nle-Trp-2'-Nal-NH_2				15	
2217	H-Tyr-D-Nle-Trp-Trp-NH_2				>5	
2462	H-Tyr-D-Nva-Phe-Phe-NH_2				2.7	>100
2463	H-Tyr-D-Ser-Phe-Phe-NH_2	2.2		13	0.5	>100
2464	H-Tyr-D-Val-Phe-Phe-NH_2				>10	
2465	H-Tyr-D-Leu-Phe-Phe-NH_2				> 10	

On page 27-28 of the specification, Claim 1 was amended as follows:

1. A compound of having the chemical structure of formula (A):



(A)

with peripheral analgesic effect, wherein:

a) X is selected from the group consisting of H and C_{1-6} alkyl;

b) Y and Z are independently selected from the group consisting of H, cyclic aralkyl, and C_{1-6} alkyl;

c) R_1 is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;

d) R_2 is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;

e) R_3 is an aromatic amino acid;

f) R_4 is an aromatic amino acid residue;

g) Q is an amide bond or an interposed amide bond mimetic;

h) with the proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_3 is phenylalanine;

then R_4 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$ or $4N_3$;

i) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is phenylalanine;

then R_4 is not unsubstituted phenylalanine or phenylalanine substituted

j) with the further proviso that when:

i) R_1 is a tyrosyl residue:

ii) R_2 is D-alanine:

iii) X, Y, and Z are H; and

iv) R_4 is 1'-naphthylalanine:

then R_3 is not 1'-naphthylalanine or 2'-naphthylalanine;

k) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine; and

iii) X, Y and Z are H,

then both R_3 and R_4 are not tryptophan;

l) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and

iii) R_4 is a neutral amino acid,

then R_3 is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

H-Tyr-D-Phe-Phe-Phe-NH_2;

H-Tyr-D-NMePhe-Phe-Phe-NH_2;

H-Tyr-D-Tic-Phe-Phe-NH_2;

H-Tyr-Pro-Phe-Thr(Bzl)-NH_2; (SEQ ID NO:2)

H-Tyr-Pro-Phe-Phe-NH_2; (SEQ ID NO:1)

H-Tyr-Pro-Phe-Apb-NH_2;

H-Tyr-Pro-Phe-App-NH_2;

H-Tyr-Pro-Phe-Aph-NH_2; and

H-Tyr-Pro-Apb-Phe-NH_2;

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic

On page 32-33 of the specification, Claim 15 was amended as follows:

15. A compound selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-2'-Nal-NH_2;

H-Tyr-D-Ala-D-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe($4NO_2$)-Phe($4NO_2$)-NH_2;

H-Tyr-D-Ala-Phe-Tic-NH_2;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH_2;

H-Tyr-D-Ala-Phe-1'-Nal-NH_2;

H-Tyr-D-Ala-Trp-Phe-NH_2;

H-Tyr-D-Ala-Phe-Trp-NH_2;

H-Tyr-∇Ala-Phe-Phe-NH_2; (SEQ ID NO:3)

∇CH_2-Tyr-D-Ala-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Trp-NH_2;

H-Tyr-D-Nle-Phe-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-Phe-NH_2;

H-Tyr-D-Ala-Trp-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-Trp-NH_2;

H-Tyr-D-Nva-Phe-Phe-NH_2;

H-Tyr-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Val-Phe-Phe-NH_2;

H-Tyr-D-Leu-Phe-Phe-NH_2;

H-Tyr-D-Ile-Phe-Phe-NH_2;

H-Tyr-D-Abu-Phe-Phe-NH_2[']$_2$;

H-Tyr-Chl-Phe-Phe-NH_2;

H-Tyr-Cle-Phe-Phe-NH_2;

H-Tyr-D-Arg-Phe-Phe-NH_2;

H-Tyr-D-Cys-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;

H-Tyr-D-Ala-Phe-Phg-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Hph-NH_2 bis-trifluoroacetic acid;

H-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid;

H-D-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Hph-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Cys(Bzl)-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Hph-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Arg-Phg-Phe-NH_2 bis-trifluoro acetic acid salt;

H-Tyr-D-Ala-Phe-Phe-CH_2OH hydrochloride salt;

H-Tyr-D-Ala-Hph-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Met-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-D-Phe-NH_2 bis-trifluoroacetic acid salt;.

H-Tyr-D-Ala-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-(D)-Ala-(D)-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Phe(pF)-NH_2 bis-trifluoroacetic acid salt;

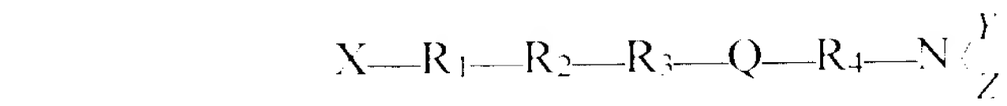
H-Tyr-D-Arg-Phe-D-Phe(pF)-NH_2 ditrifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Phe(pF)-NH_2 trifluoroacetic acid salt; and

H-Tyr-D-Ala-Phe-D-Phe(pF)-NH_2 trifluoroacetic acid salt.

On page 33-35 of the specification, claim 18 was amended as follows:

18. A pharmaceutical composition possessing analgesic activity, comprising, in admixture with a pharmaceutically acceptable carrier, an effective amount of a least one compound having the chemical structure of formula (A):



(A)

with peripheral analgesic effect, wherein:

a) X is selected from the group consisting of H and C_{1-6} alkyl;

b) Y and Z are independently selected from the group consisting of H,

c) R_2 is an amino acid having the R-configuration, dihomophenylalanine, homophenylalanine, cyclopropylalanine, cyclohomoleucine or cycloleucine;

e) R_3 is an aromatic amino acid;

f) R_4 is an aromatic amino acid residue;

g) Q is an amide bond or an interposed amide bond mimetic;

h) with the proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_3 is phenylalanine;

then R_4 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$ or $4N_3$;

i) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is phenylalanine;

then R_3 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$;

j) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is 1'-naphthylalanine;

then R_3 is not 1'-naphthylalanine or 2'-naphthylalanine;

k) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine; and

iii) X, Y and Z are H.

i) R_1 is a tyrosyl residue;

ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and

iii) R_4 is a neutral amino acid,

then R_3 is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

H-Tyr-D-Phe-Phe-Phe-NH_2;

H-Tyr-D-NMePhe-Phe-Phe-NH_2;

H-Tyr-D-Tic-Phe-Phe-NH_2;

H-Tyr-Pro-Phe-Thr(Bzl)-NH_2; (SEQ ID NO:2)

H-Tyr-Pro-Phe-Phe-NH_2; (SEQ ID NO:1)

H-Tyr-Pro-Phe-Apb-NH_2;

H-Tyr-Pro-Phe-App-NH_2;

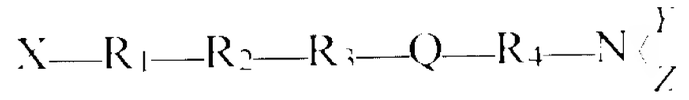
H-Tyr-Pro-Phe-Aph-NH_2; and

H-Tyr-Pro-Apb-Phe-NH_2;

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

On page 38-40 of the specification, claim 30 was amended as follows:

30. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment a pharmaceutically effective amount of at least one compound having the chemical structure of formula (A):



(A)

wherein:

a) X is selected from the group consisting of H and C_{1-6} alkyl;

b) Y and Z are independently selected from the group consisting of H,

c) R_1 is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;

e) R_3 is an aromatic amino acid;

f) R_4 is an aromatic amino acid residue;

g) Q is an amide bond or an interposed amide bond mimetic;

h) with the proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_3 is phenylalanine;

then R_4 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$ or $4N_3$;

i) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is phenylalanine;

then R_3 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$;

j) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is 1'-naphthylalanine;

then R_3 is not 1'-naphthylalanine or 2'-naphthylalanine;

k) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine; and

iii) X, Y and Z are H.

i) R_1 is a tyrosyl residue;

ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and

iii) R_4 is a neutral amino acid,

then R_3 is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

H-Tyr-D-Phe-Phe-Phe-NH_2;

H-Tyr-D-NMePhe-Phe-Phe-NH_2;

H-Tyr-D-Tic-Phe-Phe-NH_2;

H-Tyr-Pro-Phe-Thr(Bzl)-NH_2; (SEQ ID NO:2)

H-Tyr-Pro-Phe-Phe-NH_2; (SEQ ID NO:1)

H-Tyr-Pro-Phe-Apb-NH_2;

H-Tyr-Pro-Phe-App-NH_2;

H-Tyr-Pro-Phe-Aph-NH_2; and

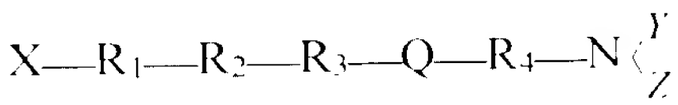
H-Tyr-Pro-Apb-Phe-NH_2;

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

On page 41-43 of the specification, claim 37 was amended as follows:

37. A method for the treatment of pain comprising the step of administering to a mammal in need of such treatment a pharmaceutically effective amount of a pharmaceutical composition possessing analgesic activity, wherein said pharmaceutical composition comprises, in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one compound having the chemical structure of formula (A):

38.



(A)

b) Y and Z are independently selected from the group consisting of H,

cyclic aralkyl, and C_{1-6} alkyl;

c) R_1 is a tyrosyl residue or a 2',6'-dimethyltyrosyl residue;

d) R_2 is an amino acid having the R-configuration, aminoisobutyric acid, cyclopropylalanine, cyclohomoleucine or cycloleucine;

e) R_3 is an aromatic amino acid;

f) R_4 is an aromatic amino acid residue;

g) Q is an amide bond or an interposed amide bond mimetic;

h) with the proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_3 is phenylalanine;

then R_4 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$ or $4N_3$;

i) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is phenylalanine;

then R_3 is not unsubstituted phenylalanine or phenylalanine substituted with

$4NO_2$;

j) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is D-alanine;

iii) X, Y, and Z are H; and

iv) R_4 is 1'-naphthylalanine;

then R_3 is not 1'-naphthylalanine or 2'-naphthylalanine;

ii) R_2 is D-alanine; and

iii) X, Y and Z are H,

then both R_3 and R_4 are not tryptophan;

l) with the further proviso that when:

i) R_1 is a tyrosyl residue;

ii) R_2 is a D-amino acid with a lower alkyl or lower thioalkyl group as a side chain; and

iii) R_4 is a neutral amino acid,

then R_3 is not unsubstituted phenylalanine;

m) and wherein said compound is not selected from the group consisting of:

H-Tyr-D-Phe-Phe-Phe-NH_2;

H-Tyr-D-NMePhe-Phe-Phe-NH_2;

H-Tyr-D-Tic-Phe-Phe-NH_2;

H-Tyr-Pro-Phe-Thr(Bz 1)-NH_2; (SEQ ID NO:2)

H-Tyr-Pro-Phe-Phe-NH_2; (SEQ ID NO:1)

H-Tyr-Pro-Phe-Apb-NH_2;

H-Tyr-Pro-Phe-App-NH_2;

H-Tyr-Pro-Phe-Aph-NH_2; and

H-Tyr-Pro-Apb-Phe-NH_2;

wherein Apb is 2-amino-4-phenylbutanoic acid, App is 2-amino-5-phenylpentanoic acid and Aph is 2-amino-6-phenylhexanoic acid.

On page 46-47 of the specification, Claim 51 was amended as follows:

51. A pharmaceutical composition having analgesic activity, comprising in admixture with a pharmaceutically acceptable carrier, an effective amount of at least one peptide selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-2'-Nal-NH_2;

H-Tyr-D-Ala-Phe-Tic-NH_2;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH_2;

H-Tyr-D-Ala-Phe-1'Nal-NH_2;

H-Tyr-D-Ala-Trp-Phe-NH_2;

H-Tyr-D-Ala-Phe-Trp-NH_2;

H-Tyr-∇Ala-Phe-Phe-NH_2; (SEQ ID NO:3)

∇CH_2-Tyr-D-Ala-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Trp-NH_2;

H-Tyr-D-Nle-Phe-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-Phe-NH_2;

H-Tyr-D-Ala-Trp-2'-Nal-NH_2;

H-Tyr-D-Ala-Trp-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-Trp-NH_2;

H-Tyr-D-Nva-Phe-Phe-NH_2;

H-Tyr-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Val-Phe-Phe-NH_2;

H-Tyr-D-Leu-Phe-Phe-NH_2;

H-Tyr-D-Ile-Phe-Phe-NH_2;

H-Tyr-D-Abu-Phe-Phe-NH_2[‘];

H-Tyr-Chl-Phe-Phe-NH_2;

H-Tyr-Cle-Phe-Phe-NH_2;

H-Tyr-D-Arg-Phe-Phe-NH_2;

H-Tyr-D-Cys-Phe-Phe-NH_2;

H-Tyr-D-Thr-Phe-Phe-NH_2;

H-Tyr-D-Thr-Phe-Phe-NH_2;

H-DMT-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;

H-Tyr-D-Ala-Phe-Phg-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Hph-NH_2 bis-trifluoroacetic acid;

H-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid;

H-D-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Hph-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Arg-Phg-Phe-NH_2 bis-trifluoro acetic acid salt;

H-Tyr-D-Ala-Phe-Phe-CH_2OH hydrochloride salt;

H-Tyr-D-Ala-Hph-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Met-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-D-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Ala-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-(D)-Ala-(D)-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Phe(pF)-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-D-Phe(pF)-NH_2 ditrifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Phe(pF)-NH_2 trifluoroacetic acid salt; and

H-Tyr-D-Ala-Phe-D-Phe(pF)-NH_2 trifluoroacetic acid salt.

On page 48-49 of the specification, claim 55 was amended as follows:

55. A method for the treatment of pain, comprising the step administering to a mammal in need of such treatment a pharmaceutically effective amount of a peptide selected from the group consisting of:

H-Tyr-Aib-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-2'-Nal-NH_2;

H-Tyr-D-Ala-D-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe($4NO_2$)-Phe($4NO_2$)-NH_2;

H-Tyr-D-Ala-Phe-Tic-NH_2;

H-Tyr-D-Ala-Phe-Phe(NMe)-NH_2;

H-Tyr-D-Ala-Phe-1'Nal-NH_2;

H-Tyr-D-Ala-Trp-Phe-NH_2;

H-Tyr-D-Ala-Phe-Trp-NH_2;

H-Tyr-∇Ala-Phe-Phe-NH_2; (SEQ ID NO:3)

∇CH_2-Tyr-D-Ala-Phe-Phe-NH_2;

H-Tyr-D-Nle-Phe-Trp-NH_2;

H-Tyr-D-Ala-Trp-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-2'-Nal-NH_2;

H-Tyr-D-Nle-Trp-Trp-NH_2;

H-Tyr-D-Nva-Phe-Phe-NH_2;

H-Tyr-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Val-Phe-Phe-NH_2;

H-Tyr-D-Leu-Phe-Phe-NH_2;

H-Tyr-D-Ile-Phe-Phe-NH_2;

H-Tyr-D-Abu-Phe-Phe-NH_2[‘];

H-Tyr-Chl-Phe-Phe-NH_2;

H-Tyr-Cle-Phe-Phe-NH_2;

H-Tyr-D-Arg-Phe-Phe-NH_2;

H-Tyr-D-Cys-Phe-Phe-NH_2;

H-Tyr-D-Thr-Phe-Phe-NH_2;

H-DMT-D-Ser-Phe-Phe-NH_2;

H-Tyr-D-Ala-Phe-Phe-OH trifluoroacetate;

H-Tyr-D-Ala-Phe-Phg-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-Hph-NH_2 bis-trifluoroacetic acid;

H-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid;

H-D-DMT-D-Ala-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Hph-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Cys(Bzl)-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Hph-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Arg-Phg-Phe-NH_2 bis-trifluoro acetic acid salt;

H-Tyr-D-Ala-Phe-Phe-CH_2OH hydrochloride salt;

H-Tyr-D-Ala-Hph-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Met-Phe-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Arg-Phe-D-Phe-NH_2 bis-trifluoroacetic acid salt;

H-Tyr-D-Ala-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-(D)-Ala-(D)-Phg-Phe-NH_2 trifluoroacetic acid salt;

H-Tyr-D-Ala-Phe-Phe(pI-)-NH_2 trifluoroacetic acid salt; and

H-Tyr-D-Ala-Phe-D-Phe(pF)-NH_2 trifluoroacetic acid salt.